Urticaria, Angioedema and Hereditary Fever Syndromes:

The Essentials for the ABAI Exam

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Overview

- Mediators
- Etiologies
- Physical Urticaria
- Chronic Idiopathic Urticaria
- Hereditary Urticaria Syndromes
- Urticarial Vasculitis
- Angioedema syndromes

Potential Mediators in Urticaria

- Histamine
  - Vasodilation, vascular permeability
- Substance P
  - Released by type C fibers by antidromic conduction
  - Vasodilator
- PGD2
  - Vasodilator
- LTC4/LTD4
  - Vascular permeability
- ?PAF
  - Vascular permeability
- C3a/C5a
- Bradykinin
  - Vasodilation
  - Vascular permeability
- Histamine releasing Factor (HRF)/β-chemokine
- Thrombin

Urticaria & Angioedema Etiologies

- Idiopathic
- Medications
  - Acute> chronic
- Stings (acute)
- Foods or additives (acute)
- Inhalation (acute)
- Infection
- Physical urticarias
- Neoplasms
- Connective tissue disease
- Endocrine
- Urticarial vasculitis
- Contact (acute)
- Transfusion reactions
- Hereditary Disorders

Connective Tissue Disease and Urticaria

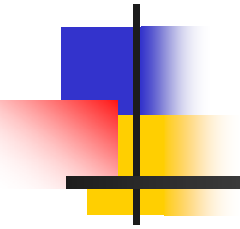
- SLE
  - < 10% patients
  - Most urticarial vasculitis
- Sjogren's
  - Majority are urticarial vasculitis
- Cryoglobulinemia
  - Hepatitis C
- Rheumatoid Arthritis?

Neoplasms and Urticaria

- Uncommon cause
  - B-cell Lymphomas and Hodkins
  - Carcinomas
    - Lung, colorectal, liver
- Schnitzler Syndrome
  - IgM monoclonal paraproteinemia
  - Nonpruritic urticaria (later may be pruritic)
  - Intermittent spiking fever
  - Arthralgias, bone pain, hyperostosis
  - Lymphadenopathy
    - anakinra effective

Parasites and Urticaria

- Helminths
  - *Ascaris, Ancylostoma, Strongyloides, Filaria, Echinococcus, Schistosoma, Trichinella, Toxocara,* and *Fasciola*
- Associated with eosinophilia



Physical Urticarias

Prime Board Exam Fodder

Cold Urticaria

- Urticaria on cold-exposed areas of the body
- Systemic reactions can occur with shock
  - Avoid swimming in lakes
- Diagnosis
  - Ice cube test
- "Drug of choice"
  - Cyproheptadine
  - Other antihistamines also work

Mechanisms of Idiopathic Cold Urticaria

- Histamine peaks 4-8 minutes after cold exposure
- Antibody mediated and passively transferred
  - IgE, IgG, IgM
- Other mediators
  - NCF, PAF, PGD2, TNF-a

Cold Urticaria Syndromes

- Idiopathic (most common)
- Secondary forms
  - Cold-dependent immunoglobulin diseases
    - Cryoglobulinemia
    - Cold agglutinin disease
    - Cryofibrinogenemia
    - Paroxysmal cold hemoglobinuria
    - Cold hemolysis
- Delayed Cold Urticaria
  - Swelling 9-18 hrs after cold exposure
  - Not passively transferred

Cold Urticaria Syndromes -2

- Localized cold urticaria
  - Certain areas of body urticate with cold exposure
  - Predisposing factors
    - Cold injury
    - Immunotherapy injection sites
    - Insect bites
- Localized cold reflex urticaria
  - Ice cube test positive but only in the vicinity of the contact site

Ice Cube Test Negative Cold Urticaria

- Cold-induced cholinergic urticaria
  - Exercise in cold air causes urticaria resembling cholinergic urticaria
  - Requires systemic cold exposure
- Systemic cold urticaria
  - Generalized hives with systemic cold exposure
  - Unrelated to exercise
- Cold-dependent dermographism
  - Accentuated hive formation if skin scratched and then chilled

Local Heat Urticaria

- Very rare
- Test tube of water @ 44 ºC to arm for 5 minutes
  - Hive forms few minutes later
- Histamine and NCF released

Cholinergic urticaria

- Occurs primarily in teenagers and young adults
- Pruritic, small macules and papules occur in response to heat, exercise, or emotional stress
  - May have other cholinergic symptoms
    - Lacrimation, salivation, diarrhea
  - May occur with wheezing
  - May occur without visible skin lesions (cholinergic pruritus)

Cholinergic urticaria

- Pathophysiologic Mechanisms
  - Neurogenic reflex
    - Placing hand in warm water with proximal tourniquet does not cause local hives
    - Removal of tourniquet leads to generalized eruption
    - Central perception of temperature change
  - Autologous sweat sensitivity
    - Sweat may cause basophil degranulation in sensitive subjects

Cholinergic Urticaria subtypes

- Non-follicular
  - Most common
  - Hypersensitivity to autologous sweat
  - Satellite wheals to acetylcholine skin test
  - Negative ASST (autologous serum skin test)
- Follicular
  - Follicular wheals
  - Weak to no response to autologous sweat
  - No satellite wheals to acetylcholine
  - Positive ASST

Fukunaga A et al. J Allergy Clin Immunol 2005;116:397-402.

Cholinergic Urticaria

- Diagnostic testing
  - Challenge by exercise or hot water (44ºC)
  - Methacholine skin testing
    - Poor specificity and sensitivity
  - Autologous sweat skin testing
    - Positive in non-follicular subtype
- Drug of choice
  - hydroxyzine

Cholinergic Urticaria with Hypotension

- Rare reports of patients with cholinergic urticaria with recurrent hypotension
  - Increase in core body temperature > 0.7 ºC with warming blankets or submersion in warm water causes urticaria, histamine release and anaphylactic symptoms
  - Patients with exercise-induced anaphylaxis will not react with passive heating

Delayed Pressure Urticaria (Angioedema)

- Symptoms develop 4-6 hrs after pressure stimulus
  - Hands, feet, buttocks
- Usually associated with non-pressure induced chronic urticaria
- "Sandbag" test
  - 5-15 lb weight applied over forearm, shoulder, thigh for 10-20 minutes
- Usually unresponsive to antihistamines
- Corticosteroids may be required

Dermographism

- Very common- affects 2-5% of population
- Small fraction of these patients will seek treatment
- Stroking of the skin results in linear wheals which may persist as long as 30 minutes
  - patients may complain of generalized pruritus or "skin crawling"
- Passive-transfer studies suggest an IgE-mediated reaction
- Associations
  - Penicillin therapy
  - Contact dermatitis
  - Other physical urticarias
  - mastocytosis

Solar Urticaria

- Rare disorder
- Brief exposure to light causes urticaria within 1-3 minutes
  - Lesions last 1-3 hrs
- Most patients in 3rd and 4th decade of life

Solar Urticaria Types

- Type I & IV
  - May be passively transferred
  - Type I protected by ordinary window glass
- Type VI
  - Erythropoietic protoporphyria
    - Protoporphyrin IX acts as a photosensitizer
    - Porphyrin in urine is normal
    - Protoporphyrin and coproporphyrin in feces are increased
- Type II, III, V
  - mechanism unknown

Aquagenic Urticaria

- Rare form of urticaria
- Patients develop small wheals with contact with water independent of temperature
- Tap/distilled water compress applied to the skin

Tests For Physical Urticaria

Cold	Ice cube test
Localized Heat	Test tube water 44ºC
Cholinergic	Exercise for 15-20 min. Leg immersion in 44ºC bath
Delayed Pressure	Sand bag test: 15 lb weight for 15 minutes
Dermographism	Stroking skin
Solar	Specific wavelength light exposure
Aquagenic	Water compress
Vibratory	Vortex for 4 minutes

Physical Urticaria: Passive Transfer by Serum

- Cold
  - IgE, IgM, IgG, cryoglobulins
- Solar Type I & IV
  - IgE ?
- Dermographism
  - IgE

Chronic Autoimmune Urticaria

- 30-40% CIU autoimmune cause
- Thyroid autoantibodies > 20% of CU pts
  - anti-thyroid peroxidase > anti-thyroglobulin Ab
- IgG or IgM antibodies against high-affinity IgE receptor
  - α chain
  - Rarely anti-IgE antibodies
- C5a augments histamine release by IgG anti-α antibodies
- Detected through autologous serum skin test and basophil histamine release assays

Chronic Idiopathic Urticaria

- After exclusion of acute urticaria and physical urticarias, identifiable etiologies may be found in < 2% cases according to Kaplan
- Skin biopsy
  - Nonnecrotizing perivascular mononuclear cell infiltrate
  - Primarily lymphocytes
  - Increased mast cells in some but not all studies
  - Similar to late-phase allergic reactions except
    - Less basophils, variable eosinophils, prominent monocytes and lymphocytes

Hereditary Urticaria & AE Syndromes

- Cryoprinopathies
- Hereditary Vibratory Angioedema
- Factor I Deficiency
- Estrogen Dependent/Associated Inherited Angioedema
- Hereditary Angioedema

Cryopyrinopathies

- *C1AS1* gene encodes the protein cryopyrin (NALP3)
- Cryopyrin is a key component of the inflammasome
- Inflammasome is an intracellular complex that senses "danger" signals and activates IL-1β
- Mutations in *C1AS1* cause
  - Familial cold autoinflammatory syndrome
  - Muckle-Wells syndrome
  - NOMID
- All autosomal dominant

"Familial Cold Urticaria"

Familial Cold Autoinflammatory Syndrome (FCAS)

- Mutations in cold-induced autoinflammatory syndrome 1 gene (*CIAS1*)
- Symptoms upon exposure to cold
  - Burning papular lesions
  - Fever, chills
  - Arthralgias, myalgias, conjunctivitis, headache, leukocytosis
  - Ice cube test negative

Muckle-Wells Syndrome

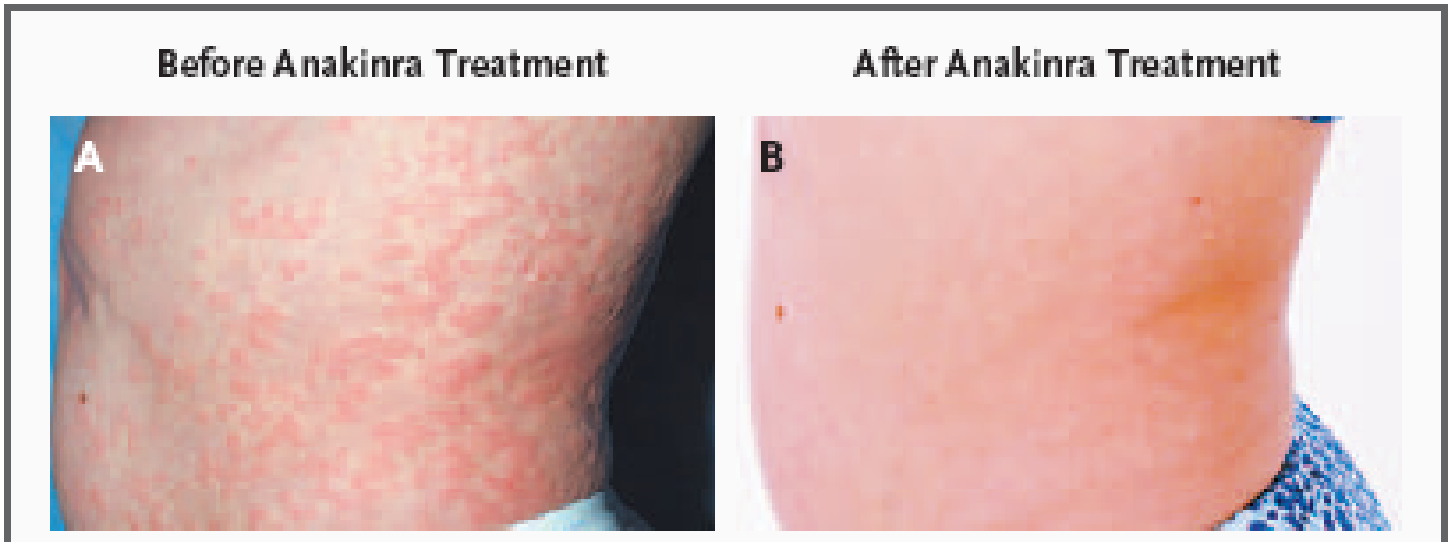
- CIAS1 gene mutations
- Familial urticaria
  - urticarial vasculitis and cold urticaria reported
- Renal amyloidosis
- Deafness
- Polyarthralgias

NOMID

- Neonatal-onset multisystem inflammatory disease (NOMID)
  - a.k.a. chronic infantile neurologic cutaneous articular syndrome (CINCA)
- Most children have mutations in *C1AS1*
- Clinical Features
  - Urticaria-like rash within 1st 6 weeks of life
  - Bony overgrowth
  - CNS manifestations
    - Chronic aseptic meningitis, mental retardation, cerebral atrophy, chronic papilledema, SNHL, etc.

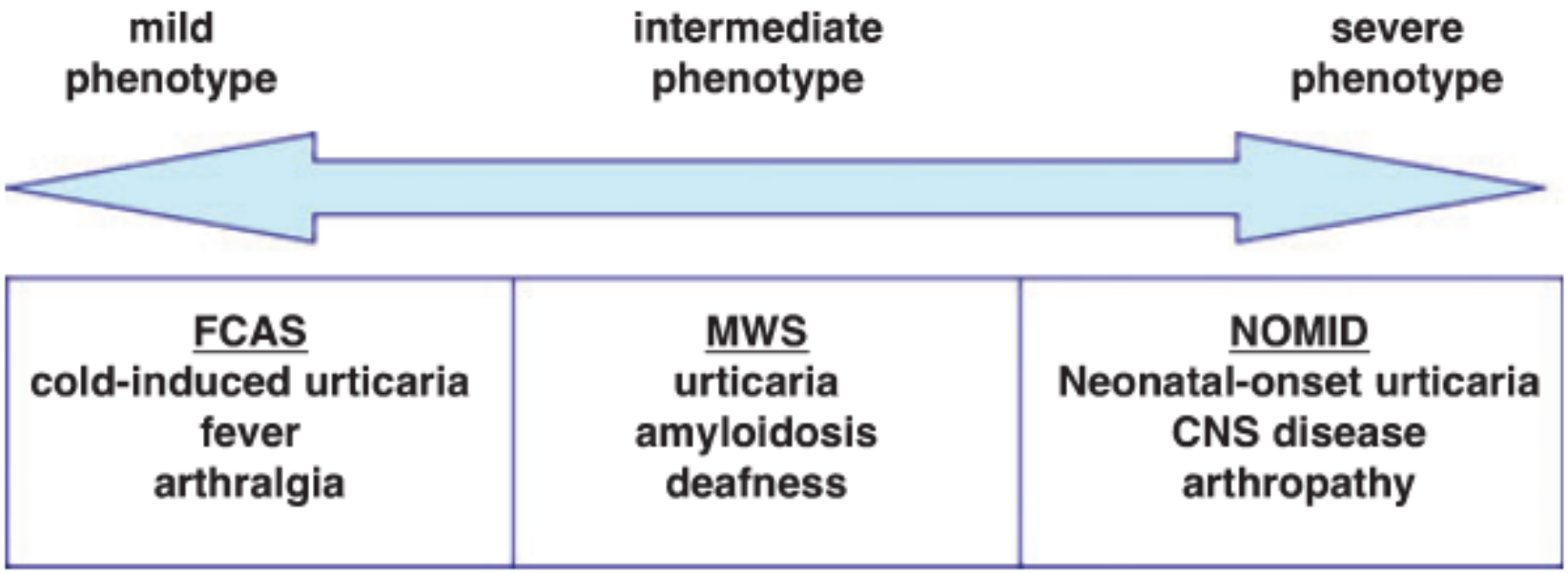
NOMID

- Laboratory
  - ↑ WBC, ↑ amyloid A, ↑ ESR
- Therapy
  - IL-1 receptor antagonist (anakinra)



N Engl J Med 2006;355:581-92.

Spectrum of Cryopyrinopathies



Shinkai K et al. Clin Derm 2007;33:1-9.

Autoinflammatory Syndromes

- Cryoprinopathies
- Familial Mediterranean Fever
- Hyper IgD syndrome
- TRAPS
- Blau syndrome
- Chrohn's
  - Non-Mendelian inheritance
  - Recurrent fevers not a feature

Systemic Autoinflammatory Disorders

- Familial Mediterranean Fever
  - Autosomal recessive
  - Pyrin mutations
  - Erysipeloid erythema, abdominal pain, arthritis, pleuritis, amyloidosis
- Hyper IgD syndrome
  - Autosomal recessive
  - Mevalonate kinase mutations; ↑ IgD
  - Maculopapular rash, abdominal pain, cervical adenitis

Systemic Autoinflammatory Disorders

- TRAPS (TNF receptor associated periodic syndrome
  - *TNFRSF1A* mutations; autosomal dominant
  - fever, abdominal pain, pleurisy, migrating erythema, periorbital edema, conjunctivitis, amyloidosis
- Blau Syndrome
  - *CARD15 (NOD2)* mutation; autosomal dominant
  - Fever, granulomatous arthritis, uveitis, erythematous papular rash, camptodactyly

Hereditary Vibratory Angioedema

- Autosomal dominant
  - Nonfamilial cases also reported
- Pruritus and swelling within minutes of vibratory stimuli
- Diagnosed by using a lab vortex for 4 minutes
- Histamine elevated after vibratory stimulus
- Antihistamines partially beneficial

Factor I Deficiency (C3b inactivator)

- Rare disorder
- Autosomal recessive
- May present with urticaria
- Depressed C3 levels
  - May have liberation of C3a anaphylatoxin

Urticaria Pharmacotherapy

- Antihistamines
  - H_1 receptor antagonists
  - H_2 receptor antagonists
- Leukotriene antagonists
- Oral corticosteroids
- Cyclosporine, tacrolimus
- Others
  - omalizumab, dapsone, hydroxychloroquine, colchicine, sulfasalazine, IVIG, androgens, methotrexate, cyclophosphamide, androgens, gold, phototherapy, plasmapheresis

Urticarial Vasculitis

- Prevalence ~5% CIU
- Female predominance
- Peak incidence 4th decade
- Histopathology can be indistinguishable from leukocytoclastic vasculitis (palpable purpura)
  - Leukocytoclasis
  - Vessel wall damage
  - +/- Fibrin deposits or RBC extravasation
- Immunofluorescence
  - Igs, Complement, fibrin within vessel wall

Davis MD, Brewer J. Immunol Allergy Clin N Am 2004;24:183-213.

Clinical Features of UV

- Urticaria description
  - Painful, tender, burning or pruritic
- Duration of lesions
  - 24-72 hrs
- Lesions resolve with purpura or hyperpigmentation

Hypocomplementemic urticarial vasculitis syndrome (HUVS)

- More serious and systemic form of UV
  - Death due to vasculitis rare
- Urticaria and hypocomplementemia
- Associated features
  - Angioedema (50%)
  - Obstructive lung disease (50%)
  - Uveitis, episcleritis (30%)
  - Arthralgia, arthritis
  - Mild glomerulonephritis
  - Recurrent abdominal pain
  - Cardiac disease (rare)
  - Neurologic problems (e.g. pseudotumor cerebri)
    - All of above features can be seen with normocomlementemic UV but are more common with HUVS

Laboratories in HUVS

- Hypocomplementemia
  - ↓ C3 or C4
  - ↓ ↓ C1q
- Anti C1q antibodies (most all patients)
  - Relatively specific for HUVS and SLE
- 50% ANA +
  - dsDNA –
- ↑ ESR

Urticarial Vasculitis

- Etiology
  - Idiopathic most common
  - SLE, Sjogrens
  - Numerous other rare causes
- Treatment
  - Antihistamines (help with pruritus)
  - Dapsone, colchicine, hydroxychloroquine, indomethacin
  - Corticosteroids
  - Azathioprine, methotrexate, cyclosporine, cyclophosphamide, mycophenolate
- Prognosis
  - Average duration 3-4 years
  - UV typically has benign course
  - HUVS has a worse prognosis
    - COPD common cause of morbidity and mortality

ACE-I Angioedema

- Occurs in 0.1-0.7%
  - more common in African-Americans
- Usually delayed in onset
  - Mean 1.8 yrs (Malde 2007)
- Likely des-Arg bradykinin induced
  - ACE (kinase II) activates bradykinin and angiotensin I
- Usually tolerate ARBs but case reports of AE with ARBs too

Estrogen Dependent/Associated Inherited Angioedema (aka HAE type III)

- Extremely rare
- Women with recurrent AE episodes
  - Autosomal dominant?
- Normal C1-INH antigenic and function levels
- No mutations identified in C-INH gene
- Estrogen Dependent
  - AE only during pregnancy or supplemental estrogen
- Estrogen Associated
  - AE exacerbated by estrogen but occurs at other times

C1-INH

- C1-INH belongs to family of serine protease inhibitors (serpins) and inhibits:
  - C1s and C1r (classical pathway)
  - Mannin-binding lectin-associated serine proteases (MASPs)
  - FXIa (intrinsic pathway of coagulation)
  - FXIIa and kallikrein (contact system)
  - Weakly inhibits
    - Thrombin, plasmin, tissue-type plasminogen activator
- C1-INH gene
  - Chromosome 11
  - > 150 mutations identified over entire length of coding sequence

Hereditary Angioedema

- Clinical characteristics
  - Autosomal dominant
  - Acute attacks
    - Symptoms progress over 24-48 hours and resolve over the next 48 hours
    - angioedema of extremities, face, throat
    - abdominal pain, nausea, vomiting, diarrhea
    - no urticaria or pruritus
    - Symptoms not helped by antihistamines
    - May be precipitated by trauma
      - dental work
  - Hormonal effects variable

Hereditary Angioedema

- Associated conditions
  - SLE and autoimmune disorders (?)
  - Other cutaneous findings (26% in survey by Frank et al)
    - Erythematous mottling
    - Ertythema multiforme
    - Erythema marginatum

Hereditary Angioedema

- Type I
  - ~ 85% patients with C1-INH deficiency
  - Defective expression of 1 allele of C1-INH gene
  - Low C1 INH antigenic and function
- Type II
  - ~ 15 % patients with C1-INH deficiency
  - Dysfunctional mutant protein
  - C1-INH antigenic levels nl or high, functional levels decreased

Hereditary Angioedema Pathophysiology

- Bradykinin most likely mediator involved
  - Evidence in both HAE and AAE
- C2-kinin evidence weak

Acquired Angioedema (AAE)

- Clinical presentation similar to HAE except not hereditary and later onset (4th decade of life or later)
- Increased consumption of C1-INH and hyperactivation of classical complement
  - Consumption by neoplastic lymphatic tissue
  - Autoantibodies to C1-INH impair C1-INH function
    - May enhance cleavage to non-functional but antigenic protein
    - In this case C1-INH levels are normal

Acquired Angioedema (AAE)

- "Type I" (paraneoplastic)
  - B cell lymphoproliferative disease
  - MGUS (monoclonal gammopathy of unknown significance)
    - May also have autoantibody to C1-INH at some time in course of disease
- "Type II" (autoimmune)
  - Otherwise healthy
  - Autoantibody to C1-INH always present

Laboratories in Hereditary and Acquired Angioedemas

	C1-INH level	C1-INH function	C1q	C4	C3
HAE-I	↓	↓	**N**	↓	**N**
HAE-II	**N or** ↑	↓	**N**	↓	**N**
EDIAE	**N**	**N**	**N**	**N**	**N**
AAE-I	↓	↓	↓	↓	**N or** ↓
AAE-II	↓ **or N**	↓	↓ **or N**	↓	**N or** ↓

EDIAE: Estrogen-dependent inherited angioedema

Treatment Options for C1-INH Deficiencies

- Acute AE
  - Basics
    - Airway management
    - Hydration
    - Pain relief
  - C1-INH concentrate
  - Anti-fibrinolytics (+/-)
  - FFP (?)
- Short-term prophylaxis
  - Androgens 3-5 days prior
  - FFP, C1-INH concentrate, anti-fibrinolytics
- Long-term prophylaxis
  - Attenuated Androgens
    - Danazol, stanozolol, oxandrolone
  - Antifibrinolytics
    - ε-aminocaproic acis (Amicar)
    - Tranexamic acid
  - C1-INH concentrate
- Future therapies
  - r-C1-INH
  - Bradykinin receptor antagonist
  - Kallikrein inhibitors

Issues with Therapies for HAE

- Attenuated androgens
  - Adverse effects
    - Hepatotoxicity (rarely liver carcinoma)
    - Weight gain, menstrual irregularities, ↓ libido, virilization, acne, myalgias, fatigue, headache, hypertension
  - Contraindications
    - Pregnancy, lactation, childhood*, prostate CA
- Antifibrinolytics
  - Thrombosis, postural hypotension, myalgias, myositis

Therapy for AAE

- Treatment of underlying disease
  - May result in biochemical/clinical remission of AAE
- Androgens
  - AAE frequently resistant
- Antifibrinolytics
  - May be preferred over androgens
- C1-INH concentrate
  - May require higher doses and be more resistant to treat than HAE